

Amendments to the Specification:

On page 7, replace the paragraph beginning at line 7 and ending at line 14 with the following:

In another aspect, the invention includes a method of identifying a compound effective to enhance hypoxic or ischemic damage in a cell. A $\psi\delta$ RACK agonist agonist peptide is contacted with a δ PKC peptide containing a RACK binding site in the presence and absence of a test compound. The test compound is identified as being effective to enhance ischemic damage if (i) binding in the presence of the test compound is decreased relative to binding in the absence of the test compound, or (ii) the catalytic activity of the δ PKC in the presence of the test compound is increased relative to the catalytic activity in the absence of the test compound.

On page 14, replace the paragraph beginning at line 15 and ending at line 31 with the following:

In studies performed in support of the present invention to identify peptide sequences for activation and inhibition of δ PKC, the sequence of δ PKC was compared to the sequence of θ PKC, since of the three other novel PKC isozymes, δ PKC is most similar to θ PKC with a 52% identity of amino acid sequence (Osada, S.-I *et al.*; Baier, G. *et al.*). It was also assumed that each PKC isozyme should interact with a different RACK. Since the first variable (V1) domain of δ PKC contains the RACK-binding site (Johnson *et al.* 1996a) regions least similar to θ PKC may be involved in RACK binding. Fig. 1 compares the sequences of the V1 domain of rat δ PKC (SEQ ID NO:2; accession no. KIRTCD) and mouse θ PKC V1 domain (SEQ ID NO:3, accession no. Q02111). Three regions in the V1 domain of δ PKC were identified with only ~10% identity to θ PKC. These regions are indicated in Fig. 1 by the bars above the sequence of δ PKC and are referred to herein as δ V1-1 having a sequence identified herein as SEQ ID NO:4 (SFNSYELGSL), δ V1-2 having a sequence identified herein as SEQ ID NO:5

(ALTTDRGKLV), and $\psi\delta$ RACK having a sequence identified herein as SEQ ID NO:6 (MRAAEDPM). Not shown in Fig. 1 is yet another sequence identified from the δ PKC sequence for testing of its activation or inhibition of δ PKC. This sequences is identified as SEQ ID NO~~7~~ NO:7 and is referred to herein as δ V1-5.

Replace the paragraph beginning on page 14 at line 32 and ending on page 15, line 15 with the following:

As described in Example 1, the δ V1-1 and $\psi\delta$ RACK peptides were analyzed to determine whether the peptides had activity, and if so, whether the activity was as an agonist or an antagonist of δ PKC. As will be shown, δ V1-1, δ V1-2 and δ V1-5 are δ PKC antagonists and $\psi\delta$ RACK is a δ PKC agonist. In these studies, the δ V1-1 and $\psi\delta$ RACK peptides were modified with a carrier peptide by cross-linking via an N-terminal Cys-Cys bond to the *Drosophila* Antennapedia homeodomain (SEQ ID NO:8; Théodore, L., et al.; Johnson, J. A. et al., 1996b). In other studies, not described here, the peptide was modified with Tat (SEQ ID NO:9) or with polyarginine (Mitchell et al., 2000; Rothbard Rothbard et al., 2000) and gave results similar to those described herein. Details of the study are set forth in Example 1. In brief, the Antennapedia-conjugated peptides were introduced to cardiac cells at a concentration of 500 nM in the presence and absence of phorbol 12-myristate 13-acetate (PMA) or in the presence of each other. Translocation of δ PKC isozyme was assessed by Western blot analysis cystosolic and particulate fractions of treated cells. Subcellular localization of δ PKC isozyme was assessed by immunofluorescence by probing the blot with anti- δ PKC, anti- α PKC, and anti- ϵ PKC antibodies. Translocation was expressed as the amount of isozyme in the particulate fraction over the amount of isozyme in non-treated cells. The results are shown in Figs. 2-4.

Replace the paragraph on page 15, lines 16-23 with the following:

Figs. 2A-2B show the results for the cells treated with δ V1-1 in the presence (+) and absence (-) of PMA. Fig. 2A is the Western blot autoradiogram of soluble (S) and

particulate (P) cell fractions after treatment with the peptide and after probing with anti- δ PKC and anti- ϵ PKC antibodies. Fig. 2B shows the translocation of δ PKC expressed as the amount of isozyme in the particulate fraction over the amount of isozyme in non-treated cells. The δ V1-1 peptide inhibited PMA-induced δ PKC translocation. In other studies ~~not~~ shown here, the δ V1-1 peptide did not inhibit the translocation of ϵ PKC or α PKC.

Replace the paragraph on page 22, lines 10-25 with the following:

For δ V1-1, potential modifications include the following changes shown in lower case: tFNSYELGSL (SEQ ID NO:34), aFNSYELGSL (SEQ ID NO:35), SFNSYELGtL (SEQ ID NO:36), including any combination of these three substitutions, such as tFNSYELGtL (SEQ ID NO: 37). Other potential modifications include SyNSYELGSL (SEQ ID NO:38), SFNSfELGSL (SEQ ID NO:39), SNSYdLGSL (SEQ ID NO:40), SFNSYELpSL (SEQ ID NO:41). Other potential modifications include changes of one or two L to I or V, such as SFNSYEiGSv (SEQ ID NO:42), SFNSYEvGSi, (SEQ ID NO:43) SFNSYELGSv (SEQ ID NO:44), SFNSYELGSi (SEQ ID NO:45), SFNSYEiGSL (SEQ ID NO:46), SFNSYEvGSL (SEQ ID NO:47), aFNSYELGSL (SEQ ID NO:48), and any combination of the above-described modifications. Fragments and modification of fragments of δ V1-1 are also contemplated, such as YELGSL (SEQ ID NO:49), YdLGSL (SEQ ID NO:50), fDLGSL fdLGSL (SEQ ID NO:51), YDiGSL YdiGSL-(SEQ I, iGSL (SEQ ID NO:59)D-NO:52), YDvGSL YdvGSL (SEQ ID NO:53), YDLpsL YdLpsL (SEQ ID NO:54), YDLgIL YdLgIL (SEQ ID NO:55), YdLGSI (SEQ ID NO:56), YdLGSv (SEQ ID NO:57), LGSL (SEQ ID NO:58), iGSL (SEQ ID NO:59), vGSL (SEQ ID NO:60), LpSL (SEQ ID NO:61), LGIL (SEQ ID NO:62), LGSi (SEQ ID NO:63), LGSv (SEQ ID NO:64).

Replace the paragraph on page 23, lines 11-12 with the following:

Accordingly, the term "a δ PKC antagonist" as used herein intends a δ PKC peptide, which refers to any a δ V1-1 peptide, a δ V1-2 peptide and a δ V1-5 peptide.

Replace the paragraph on page 26, lines 11-19 with the following:

The plate is then incubated with a blocking solution (containing, for example bovine serum albumin) and then washed several times. A solution containing reporter-labelled (e.g., radiolabelled or fluorescently-tagged) peptide δV1-1 (SEQ ID NO: 4) and, in the test wells, as opposed to the control wells, a test compound is added. Different wells may contain different test compounds or different concentrations of the same test compound. Each test compound at each concentration is typically run in duplicate and each assay is typically run with negative (wells with no test compound) as well as positive (wells where the "test compound" is unlabeled peptide) controls. The free peptide is then washed out, and the degree of binding in the wells is assessed.

Replace the paragraph on page 26, lines 20-25 with the following:

A test compound is identified as active if it decreases the binding of the peptide, i.e., if its effect on the extent of binding is above a threshold level. More specifically, if the decrease in binding is a several-fold different between the control and experimental samples, the compound would be considered as having binding activity. Typically, a 2-fold or 4-fold threshold difference in binding between the test and control samples is sought.